

REMARKS

Claims 1, 2, 26, 37-42 constitute the pending claims in the present application. Claims 25, 27, 35, and 36 are cancelled without prejudice and Applicants reserve the right to prosecute the subject matter of claims as originally filed in the present or future applications. Claim 1 is amended to recite the small organic molecule originally recited in claim 27, and claim 27 is now cancelled. Claim 1 is also amended to recite "wherein said angiogenesis includes increased expression of vascular endothelial growth factor (VEGF)". This amendment is supported throughout the specification (e.g., Example 4, pages 101-106). Claims 26, 37, and 38 are amended to correct claim dependency in view of cancellation of claims 25 and 27. In addition, claim 25 is amended to recite "750 amu" instead of "2500 amu". Support for this amendment is found in the specification, for example on page 71, lines 6-9. Accordingly, the claim amendments introduce no new matter. Applicants' cancellation of and amendments to the claims are made without prejudice.

Applicants add new claims 43-57. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Specific support can be found, for example, on pages 71-73 of the specification.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

1. Claims 1-2, 25-26, 35-36, and 39-42 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner states that the application "fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus" of hedgehog agonists. The Examiner continues by stating "the specification provides neither a representative number of agonists that encompass the genus of hedgehog agonist, which promote angiogenesis. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus" (page 4 of the office action).

Applicants respectfully traverse. The claimed invention relates to methods of improving myocardial function comprising administering a hedgehog agonist. The claims are not directed to hedgehog agonists themselves, but rather to *methods of using* hedgehog agonists. The

specification provides specific examples of hedgehog agonists that may be used in the claimed methods (for example, polypeptides, small molecules, etc.) as well as functional features and characteristics of hedgehog polypeptide and small molecule agonists (see, for example, page 58, lines 6-12; page 58, line 24-page 59, line 4; pages 71-79). Further, the specification describes biological activities of hedgehog agonists on pages 4-5. The specification clearly contemplates use of a wide range of hedgehog agonists possessing the disclosed functional features and biological activities. Given the detailed description of numerous exemplary hedgehog agonists, as well as the functional properties and biological activities possessed by hedgehog agonists suitable for use in the claimed methods, Applicants contend that the claimed invention is sufficiently described and satisfies the written description requirement.

Nevertheless, to expedite prosecution of claims directed to certain embodiments of Applicants' invention, Applicants have amended claim 1 to more particularly point out that the hedgehog agonist is a small molecule having a structure represented by the general formula XII. Applicants' amendment is not in acquiescence to this or other grounds of rejection raised in this Office Action. Applicants reserve the right to prosecute claims of similar or differing scope. Applicants note that general formula XII and its use in the subject methods are described in the specification, and that the claimed invention satisfies the written description requirement. Reconsideration and withdrawal of this rejection is requested.

2. Claims 1-2 and 25 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Baron et al. (WO 98/35020, Baron et al.). Applicants traverse this rejection.

The basis of the rejection appears to be page 5, lines 1-5 and page 53, lines 20-30 of Baron et al. (cited by the Examiner), which discloses that "a method is provided for treating a subject suffering from an ischemia in tissues containing mesodermally derived cells, that includes selecting an effective dose of a compound that is functionally equivalent to a gene product expressed in an extraembryonic tissue; and administering the compound to the ischemic site over an effective time so as to stimulate vascular growth." However, in order to anticipate the presently claimed invention, a single prior art reference must teach each and every element of the claimed invention (MPEP 2131): "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051,

1053 (Fed. Cir. 1978). Applicants contend that the cited passages in Baron et al. are insufficient to anticipate the claimed invention.

Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out the claimed subject matter. Specifically, Applicants have amended claim 1 to more particularly point out that the hedgehog agonist for use in the claimed method is a small molecule having the general formula XII. Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Applicants contend that Baron et al. fail to teach or suggest each and every limitation of the claimed invention (e.g., fail to teach or suggest use of small molecules having the general formula XII), and thus fail to anticipate the claimed invention. Accordingly, reconsideration and withdrawal of this rejection are requested.

3. Claims 1-2, 25-27, 35-38, and 42 are rejected under U.S.C. 103(a) as allegedly unpatentable over Porter et al. (U.S. 6,613,798, 2003) as evidenced by Pettet et al. (Proc. R. Soc. Lond. B 1996; 263: 487-1493) in view of Ferrari et al. (Basic Res. Cardiol. 1995; 90: 52-54). Applicants note that U.S. Patent 6,613,798 has a filing date which is later than the priority date of the present application and continue to contend that the declaration of Leona Ling under 37 CFR 1.131 establishes "reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application." (37 CFR 1.131(b)). Therefore, Applicants maintain that U.S. Patent 6,613,798 is not available as prior art against the present application, and that this rejection cannot stand absent Porter et al.

In addition to Applicants' contention that Porter et al. is not available as prior art, Applicants note that the combination of Porter et al., Pettet et al., and Ferrari et al. fail to satisfy the criteria necessary for rendering the claimed invention obvious. Specifically, to establish a *prima facie* case of obviousness, the following three criteria must be met: (i) there must be some suggestion or motivation to modify the reference or to combine reference teachings, (ii) there must be a reasonable expectation of success of combining the cited references to arrive at the claimed invention, and (iii) the prior art references must teach or suggest each and every limitation of the claimed invention. MPEP 2142-2143.

Ferrari et al. comment on hibernating myocardium and its revascularization but make no mention or suggestion of hedgehog agonists or the treatment of ischemic conditions. Pettet et al. teach that angiogenesis is involved in wound healing. However, Pettet et al. fail to teach or suggest that hedgehog agonists could be useful as angiogenic agents, or that myocardial function following ischemia may be improved by promoting angiogenesis. Porter et al. teach small molecule hedgehog agonists. However, Porter et al. do not teach that hedgehog agonists can be used to promote angiogenesis or to improve myocardial function. Porter et al. teach that hedgehog agonists can promote neuromuscular growth, not vascular growth. In fact, Porter et al. specifically teach that hedgehog agonists may be used in the prevention and/or reduction of the severity of neurological conditions deriving from, among other causes, vascular injury and deficits such as ischemia resulting from stroke (column 46, lines 1-7 of Porter et al.). Porter et al. do not teach that the agonists can be used to promote vascularization or angiogenesis and instead teach that hedgehog agonists are useful in regulating the growth of neurons (which could be damaged as a result of vascular injury).

No common link exists between these cited disclosures that would have motivated a person skilled in the art to combine these teachings with a reasonable expectation of success of arriving at the claimed invention. It is the teachings of the present application that provide the motivation to use hedgehog agonists in the claimed method and the reasonable expectation of successfully using hedgehog agonists in the claimed methods.

The Federal Circuit has been clear in establishing the criteria necessary for rendering an invention obvious. "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Additionally, Applicants contend that the criteria for assessing obviousness clearly articulated by the Federal Circuit precludes the cobbling together of individual references, each of which teaches elements of the claimed invention, in an attempt to amass a facsimile of the

claimed invention. For example, in reversing the district court in *Gore & Associates, Inc. v. Garlock*, the Federal Circuit stated that "the district court lost sight of the principle that there must have been something present in those teachings to suggest to one skilled in the art that the claimed invention before the court would have been obvious." *Gore & Associates, Inc. v. Garlock*, 721 F.2d 1540, 1552 (Fed. Cir. 1983). Furthermore, as a result of the district court's error, the "claims were used as a frame, and individual, naked parts of separate prior art references were employed as a mosaic to recreate a facsimile of the claimed invention." *Gore & Associates, Inc. v. Garlock*, 721 F.2d at 1553.

The Federal Circuit has reiterated these standards in more recent cases. *See, In re Kotzab*, 217 F.3d 1365 (Fed. Cir. 2000); *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332 (Fed. Cir. 2005).

Identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by applicant. *In re Kotzab*, 217 F.3d at 1370.

The 'as a whole' instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might successfully break an invention into its component parts, then find a prior art reference corresponding to each component. This line of reasoning would import hindsight into the obviousness determination by using the invention as a roadmap to find its prior art components. Further, this improper method would discount the value of combining various existing features or principles in a new way to achieve a new result-often the essence of invention. *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d at 1337.

The case law is clear. To render the claimed invention obvious, there must be a motivation to specifically combine Porter et al., Pettet et al., and Ferrari et al. to arrive at the claimed invention, and this motivation must be grounded in the prior art references themselves, not in Applicants' disclosure. It is simply not enough to identify elements of the claimed invention in individual references or to use Applicants' disclosure as the motivating force for combining the teachings of the prior art.

Applicants maintain that Porter et al. is not available as prior art. Applicants additionally contend, however, that the combined teachings of Porter et al., Pettet et al., and Ferrari et al. fail to satisfy the criteria necessary to render the claimed invention obvious. Reconsideration and withdrawal of this rejection are requested.

Claims 39-41 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over the aforementioned documents in further view of Igo et al. (US 5,681,278, 1997). Igo et al. teach administration of an agent intracoronarily. However, Igo et al. fail to overcome the deficiencies of the combined teachings of Porter et al., Pettet et al., and Ferrari et al. If an independent claim, for example independent claim 1, is nonobvious under 35 U.S.C. 103, then any claim depending therefrom (e.g., claims 39-41) is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Reconsideration and withdrawal of this rejection is requested.

Claims 26-27, 35-38, and 42 are rejected as allegedly unpatentable over Baron et al. in view of Porter et al. as evidenced by Pettet et al. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Applicants arguments above with respect to the rejection based on the combined teachings of Porter et al., Pettet et al., and Ferrari et al. are equally applicable to this rejection. Applicants reiterate for the record these arguments and the citations to the relevant case law provided above. Accordingly, Applicants contend that the Patent Office has failed to establish a *prima facie* case of obviousness.

Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out certain embodiments of the claimed invention. Specifically, Applicants have amended claim 1 to more particularly point out that the claimed method of promoting angiogenesis using an effective amount of a hedgehog agonist includes promoting increased expression of VEGF, as demonstrated by Applicants' disclosure. This element of the claimed invention is neither taught nor suggested by the cited art. Given that the combined teachings of these references fail to teach or suggest each and every element of the claimed invention, the aforementioned references fail to render obvious the claimed invention.

Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. In light of Applicants' amendments and arguments, reconsideration and withdrawal of this rejection is requested.

Claims 39-41 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Baron et al. (WO 98/35020, 1998) in view of Igo et al. (US 5,681,278, 1997). The Examiner states that Igo et al. teach a method for treating blood vessels in a mammal via intrapericardial injection.

As stated above, the Baron et al. publication fails to teach or suggest small molecules as agonists. Claim 1, as amended, and all claims that depend from claim 1 are now drawn to small molecule agonists. Igo et al. fail to overcome the deficiencies of Baron et al., and thus, the combination of Baron et al. and Igo et al. fail to teach or suggest the claimed invention.

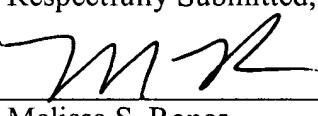
Reconsideration and withdrawal of this rejection is requested.

CONCLUSION

In view of at least the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945 under Order No. CIBT-P01-119.**

Respectfully Submitted,

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